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L1	phage adj10 antibody	1811	L1

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NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
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=> s phage(5w)antibody
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=> s l1 and antigen(5w)pepscan
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=> s l1 and pepscan
L3            0 L1 AND PEPSCAN

=> s l1 and geysen
L4            0 L1 AND GEYSEN

=> s l1 and epito?
L5          279 L1 AND EPITO?

=> s l5 and pepscan
L6            0 L5 AND PEPSCAN

=> s l5 and map?
L7           68 L5 AND MAP?

=> s l7 not 1998-2003/py
L8           25 L7 NOT 1998-2003/PY

=> d l8 1-25 ti au so py ab

L8   ANSWER 1 OF 25  CA  COPYRIGHT 2003 ACS
TI   Epitope mapping by screening of phage
     display libraries of a monoclonal antibody directed against the
     receptor binding domain of human .alpha.2-macroglobulin
AU   Birkenmeier, Gerd; Osman, Awad A.; Kopperschlager, Gerhard; Mothes, Thomas
SO   FEBS Letters (1997), 416(2), 193-196
```

CODEN: FEBLAL; ISSN: 0014-5793
PY 1997
AB The human proteinase inhibitor, .alpha.2-macroglobulin (.alpha.2-M), inhibits a large no. of proteinases, .alpha.2-M-proteinase complexes are rapidly cleared from the circulation by binding to a cellular receptor (.alpha.2-M-R/LRP) via the receptor binding domain (RBD) which is made up of a 20 kDa C-terminal stretch of the 180 kDa monomer of the inhibitor. A monoclonal antibody (mab .alpha.-1) has been described which reacts with the receptor-recognizable form of the inhibitor, the so called transformed .alpha.2-M (.alpha.2-Mt). By screening of a phage display library an **epitope** in the RBD of the inhibitor was identified that reacts with mab .alpha.-1. Out of 25 phage clones a heptapeptide sequence (S-x1-x2-D-x3-x4-K) was obtained contg. identical amino acids in three positions. A consensus peptide (S-R-S-D-P-P-K) was synthesized and found to displace .alpha.2-Mt from binding to mab .alpha.-1 and to receptor. The specificity of competition was demonstrated by a reversed peptide and a control antibody. By structural comparison it was found that the consensus heptapeptide mimics a discontinues conformationally constrained **epitope** present in the RBD of the inhibitor. This is the first report describing the detection of discontinuous **epitopes** by phage display using a short linear peptide.

L8 ANSWER 2 OF 25 CA COPYRIGHT 2003 ACS
TI Molecular characterization of murine humoral immune response to botulinum neurotoxin type A binding domain as assessed by using **phage antibody** libraries
AU Amersdorfer, Peter; Wong, Cindy; Chen, Steven; Smith, Theresa; Deshpande, Sharad; Sheridan, Robert; Finnern, Ricarda; Marks, James D.
SO Infection and Immunity (1997), 65(9), 3743-3752
CODEN: INFIBR; ISSN: 0019-9567
PY 1997
AB To produce antibodies capable of neutralizing botulinum neurotoxin type A (BoNT/A), the murine humoral immune response to BoNT/A binding domain (HC) was characterized at the mol. level by using **phage antibody** libraries. Mice were immunized with BoNT/A HC, the spleens were harvested, and single-chain Fv (scFv) **phage antibody** libraries were constructed from the Ig heavy and light chain variable region genes. Phage expressing BoNT/A binding scFv were isolated by selection on immobilized BoNT/A and BoNT/A HC. Twenty-eight unique BoNT/A HC binding scFv were identified by ELISA and DNA sequencing. **Epitope mapping** using surface plasmon resonance in a BIAcore revealed that the 28 scFv bound to only 4 nonoverlapping **epitopes** with equil. consts. (Kd) ranging from 7.3 .times. 10-8 to 1.1 .times. 10-9 M. In a mouse hemidiaphragm assay, scFv binding **epitopes** 1 and 2 significantly prolonged the time to neuroparalysis, 1.5- and 2.7-fold, resp., compared to toxin control. ScFv binding to **epitopes** 3 and 4 showed no protection against neuroparalysis. A combination of scFv binding **epitopes** 1 and 2 had an additive effect on time to neuroparalysis, which increased to 3.9-fold compared to the control. The results suggest that there are two "productive" receptor binding sites on HC which lead to toxin internalization and toxicity. Blockade of these two **epitopes** with monoclonal antibodies may provide effective immunoprophylaxis or therapy against BoNT/A intoxication.

L8 ANSWER 3 OF 25 CA COPYRIGHT 2003 ACS
TI **Mapping** the protein surface of human immunodeficiency virus type 1 gp120 using human monoclonal antibodies from phage display libraries
AU Ditzel, Henrik J.; Parren, Paul W. H. I.; Binley, James M.; Sodroski, Joseph; Moore, John P.; Barbas, Carlos F., III; Burton, Dennis R.
SO Journal of Molecular Biology (1997), 267(3), 684-695
CODEN: JMOBAK; ISSN: 0022-2836
PY 1997
AB Panels of hybridoma-derived monoclonal antibodies against diverse **epitopes** are widely used in defining protein surface topog.,

particularly in the absence of crystal or NMR structural information. Here the authors show that recombinant monoclonal antibodies from phage display libraries provide a rapid alternative for surface **epitope mapping**. Diverse **epitopes** are accessed by presenting antigen to the library in different forms, such as sequential masking of **epitopes** with existing antibodies or ligands prior to selection and selection on peptides. The approach is illustrated for a recombinant form of the human immunodeficiency virus type 1 (HIV-1) surface glycoprotein gp120 which has been extensively **mapped** by rodent and human monoclonal antibodies derived by cellular methods. Human recombinant Fab fragments to most of the principal **epitopes** on gp120 are selected including Fabs to the C1 region, a C1/C5 **epitope**, a C1/C2 **epitope**, the V2 loop, the V3 loop and the CD4 binding domain. In addn. an **epitope** linked to residues in the V2 loop and CD4 binding domain is identified. Most of these specificities are assocd. with **epitopes** presented poorly on native multimeric envelope, consistent with the notion that these antibodies are assocd. with immunization by forms of gp120 differing in conformation from that found on whole or infected cells.

L8 ANSWER 4 OF 25 CA COPYRIGHT 2003 ACS
TI Human recombinant antibody fragments specific for a rye-grass pollen allergen: characterization and potential applications
AU De Lalla, Claudia; Tamborini, Elena; Longhi, Renato; Tresoldi, Eleonora; Manoni, Marco; Siccardi, Antonio G.; Arosio, Paolo; Sidoli, Alessandro
SO Molecular Immunology (1996), 33(13), 1049-1058
CODEN: MOIMD5; ISSN: 0161-5890
PY 1996
AB One of the major allergens from the pollen of perennial rye grass (Lolium perenne), Lol pII, was used to isolate specific antibody fragments from a random combinatorial library displaying a large repertoire of human Fab on filamentous phages. After five panning cycles on recombinant Lol pII immunotubes, **phage** binders were isolated and the **antibody** fragments expressed as sol. Fab mols. in the Escherichia coli periplasm. The DNA sequencing of the clones producing antibodies with the highest binding activity showed three of them to be identical, while one differed by two amino acid substitutions in the heavy chain. The antibody fragments were produced in milligram amts., affinity-purified and further characterized. They bound the natural allergen as well as the recombinant one, with no cross-reactivity with other allergens contained in the pollen ext. of L. perenne. One antibody bound the allergen with Kd = 2.63 .times. 10-9 M, as demonstrated by the surface plasmon resonance technique, and was able to compete with a fraction of serum IgE. **Epitope mapping** using synthetic peptides revealed that antigenic domains, located between amino acids 39 and 51 of Lol pII, are recognized by Fab and polyclonal IgE from sera of allergic donors. The Fab fragments inhibited the binding of serum IgE to the allergen. In vitro expts. on whole blood from allergic subjects showed that recombinant Fab fragments had a blocking activity on histamine release from cells challenged with recombinant Lol pII allergen. Thus, serum IgE and recombinant Fab fragments recognize common **epitopes**, although they represent the outcome of different maturation and/or selection processes. Our mol. and functional findings indicate that allergen-specific human antibodies may be useful for the characterization of the antigenic structure of allergens. We conclude that a phage library is a powerful source of anti-allergen human antibodies with high affinity and high specificity. Moreover, these mols. may be potentially innovative reagents for the treatment of atopic allergy.

L8 ANSWER 5 OF 25 CA COPYRIGHT 2003 ACS
TI Antibodies against HIV-1 from phage display libraries: **mapping** of an immune response and progress towards antiviral immunotherapy
AU Parren, Paul W.H.I.; Burton, Dennis R.
SO Chemical Immunology (1997), 65(Antibody Engineering), 18-56
CODEN: CHMIEP; ISSN: 1015-0145

SO Journal of Molecular Biology (1995), 248(1), 58-78
CODEN: JMOBAK; ISSN: 0022-2836
PY 1995
AB The authors previously described the use of a phage-displayed library of random hexapeptides to define and localize the **epitope** on the human tumor suppressor protein p53 recognized by the monoclonal antibody PAb240. Here the authors have extended these results to a further eight anti-p53 monoclonal antibodies and to two further libraries, which display 12-mer and 20-mer peptides, resp. First, the authors showed that selection of PAb240 binding clones from the 12-mer and 20-mer libraries gives essentially identical results to those obtained by screening the 6-mer library. Second, the authors used the 6-mer and 12-mer libraries to define the detailed specificity profiles of six antibodies (DO-1, DO-2, DO-7, Bp53-11, Bp53-12 and Bp53-19), which recognize the same short, highly immunogenic N-terminal segment of p53. Finally, the authors employed all three libraries to reveal the distinct mechanisms by which PAb421 and PAb122, two monoclonal antibodies that allosterically activate sequence-specific DNA binding by p53, react specifically with the same pos.-charged C-terminal segment. In each case the **epitope** locations inferred from the selected sequences were confirmed by probing an array of overlapping synthetic peptides representing the primary sequence of p53. The results emphasize the consequences for **epitope mapping** of screening random, as opposed to antigen-derived, peptide libraries, specifically (1) that comparison of selected sequences reveals the contribution of individual residues to binding energy and specificity; (2) that heteroclitic reactions can lead to definition of a consensus that is related to but distinct from the immunizing **epitope** and (3) that isolation of non-immunogen-homologous "mimotope" sequence reveals discrete, alternative ligand structures. The results with PAb421 and PAb122 provide examples where, while selection from the 12-mer and 20-mer libraries leads to isolation of immunogen-homologous sequences, selection from the 6-mer library results in the isolation either of no binding clones (PAb122) or solely of "mimotope" sequences with no discernible homol. to the original antigen (PAb421). In addn. the results with PAb421 reveal that linear **epitopes** can be longer than previously thought and can be formally discontinuous, consisting of independent contact motifs, which show promiscuous relative positioning.

L8 ANSWER 9 OF 25 CA COPYRIGHT 2003 ACS
TI Screening a monoclonal antibody with a fusion-phage display library shows a discontinuity in a linear **epitope** within PreS1 of hepatitis B virus
AU Germaschewski, Volker; Murray, Kenneth
SO Journal of Medical Virology (1995), 45(3), 300-5
CODEN: JMVIDB; ISSN: 0146-6615
PY 1995
AB The **epitope** recognized by the monoclonal antibody MA18/7, specific for the PreS1-domain of the hepatitis B virus surface antigen, has been defined precisely by a library of fusion-phage carrying random hexapeptides on the tip of filamentous phage fd particles. Phage, isolated after only one round of affinity selection, displayed hexapeptides showing strong conservation of the PreS1 primary sequence in the region 19-23 with three noncontiguous residues, DP (20 and 21) and F (23) appearing in **phage** that bound the **antibody**. The importance of these core residues was supported by comparing the antibody binding of individual phage in soln., which provided relative dissocn. consts. for these interactions. Replacement of F (23) by Y was the only substitution obsd. in the three core residues, and resulted in somewhat weaker binding. Synthetic tetra- and hexapeptides contg. these key residues inhibited the reaction between the **phage** and the **antibody**.

L8 ANSWER 10 OF 25 CA COPYRIGHT 2003 ACS
TI Identification of novel peptide antagonists for von Willebrand factor

binding to the platelet glycoprotein Ib receptor from a phage **epitope** library

AU South, Victoria; Searfoss, George H.; French, Stephen; Cheadle, Christopher; Murray, Edward; Howk, Richard; Jaye, Michael; Ricca, George A.

SO Thrombosis and Haemostasis (1995), 73(1), 144-50
CODEN: THHADQ; ISSN: 0340-6245

PY 1995

AB The authors have constructed a fusion phage **epitope** library in the filamentous bacteriophage fuse5. The library was made by inserting a degenerate oligonucleotide which encodes 15 variable amino acids into the NH2-terminal region of the phage gene III protein. This library, contg. over 107 different **epitope** bearing phage, has been used to identify inhibitors of the von Willebrand factor (vWF)-platelet Glycoprotein Ib interaction. The library was screened with a monoclonal antibody (RG46) that recognized the GPIb binding domain of vWF (amino acids 445-733). A total of 30 clones falling into 8 classes have been identified that react with the RG46 antibody. Isolates from all 8 classes are pos. by immunoblot anal. The amino acid sequence of the gene III fusion protein from pos. clones showed a strong homol. to the known RG46 **epitope**. Peptides identified from the screen were synthesized and used to demonstrate that some of the synthetic peptides exhibited inhibitory activity towards ristocetin induced binding of vWF to the GPIb receptor. Thus, the authors have demonstrated that screening a fusion **phage epitope** library with a monoclonal **antibody** that inhibits vWF binding to the GPIb receptor can be a useful tool not only for **mapping** antibody recognizing determinants, but also can serve as a source for identifying novel peptides that are antagonists for vWF binding to the platelet GPIb receptor.

L8 ANSWER 11 OF 25 CA COPYRIGHT 2003 ACS

TI Immunogenicity and **epitope mapping** of foreign sequences via genetically engineered filamentous phage

AU De la Cruz, Vidal F.; Lal, Altaf A.; McCutchan, Thomas F.

SO Journal of Biological Chemistry (1988), 263(9), 4318-22
CODEN: JBCHA3; ISSN: 0021-9258

PY 1988

AB Repeat regions of the circumsporozoite protein gene of Plasmodium falciparum were cloned into the pIII gene of a filamentous phage. These genetically engineered filamentous phage display the recombinant proteins on their surface. They are both antigenic and immunogenic in rabbits. The recombinant phage were useful as a source of antigen for this scarce malaria protein, for producing carrier-hapten conjugates for obtaining immunol. reagents in rabbits, and for B **epitope mapping**. In mice the antibody response to the cloned antigens seems to be controlled by immune response genes. Therefore this system also has the potential for use in helper T cell **epitope mapping** using inbred mouse strains. This advantage will be of use in vaccine development.

L8 ANSWER 12 OF 25 CA COPYRIGHT 2003 ACS

TI .lambda.Gt11: Gene isolation with antibody probes and other applications

AU Snyder, Micheal; Elledge, Stephen; Sweetser, Douglas; Young, Richard A.; Davis, Ronald W.

SO Methods in Enzymology (1987), 154(Recomb. DNA, Pt. E), 107-28
CODEN: MENZAU; ISSN: 0076-6879

PY 1987

AB Methods are described for the isolation of eukaryotic and prokaryotic genes by screening Escherichia coli expression libraries with antibody probes using phage .lambda.gt11 as an expression vector. Other uses of .lambda.gt11, such as in the prepn. of foreign proteins expressed in E. coli, **mapping epitope** coding regions, and transposon mutagenesis, are described.

L8 ANSWER 13 OF 25 CA COPYRIGHT 2003 ACS

TI Production and detection of coliphage T4 endonuclease V polyclonal and monoclonal antibodies using staphylococcal protein-A hybrid proteins
AU Valerie, Kristoffer; Fronko, Gerald; Long, Walter; Henderson, Earl E.; Nilsson, Bjoern; Uhlen, Mathias; De Riel, Jon K.
SO Gene (1987), 58(1), 99-107
CODEN: GENED6; ISSN: 0378-1119
PY 1987
AB To facilitate the prodn. of antibodies against endonuclease V, a pyrimidine dimer-specific DNA glycosylase produced in bacteriophage T4-infected Escherichia coli, plasmids contg. protein-A-endonuclease V fusion genes under control of the E. coli tac promoter were constructed. Induction with isopropyl-.beta.-D-thiogalactopyranoside produced large amts. of fusion proteins, which could easily be purified on human IgG agarose columns. The affinity-purified fusion proteins were injected into rabbits and mice to produce polyclonal and monoclonal antibodies, and also used for the screening of the monoclonal antibodies. These antibodies recognized endonuclease V on immunoblots, and also inhibited the DNA-glycosylase activity in vitro. **Epitope mapping** of monoclonal antibodies showed that they all (6/6) recognized determinants in the C-half of endonuclease V. A convenient way to detect primary antibodies on nitrocellulose was also developed using a crude protein ext. contg. protein-A-.beta.-galactosidase fusion protein and subsequent detection with a mixt. of dyes.

L8 ANSWER 14 OF 25 MEDLINE
TI **Epitope mapping** by screening of **phage** display libraries of a monoclonal **antibody** directed against the receptor binding domain of human alpha2-macroglobulin.
AU Birkenmeier G; Osman A A; Kopperschlager G; Mothes T
SO FEBS LETTERS, (1997 Oct 20) 416 (2) 193-6.
Journal code: 0155157. ISSN: 0014-5793.
PY 1997
AB The human proteinase inhibitor, alpha2-macroglobulin (a2-M), inhibits a large number of proteinases. Alpha2-M-proteinase complexes are rapidly cleared from the circulation by binding to a cellular receptor (alpha2-M-R/LRP) via the receptor binding domain (RBD) which is made up of a 20 kDa C-terminal stretch of the 180 kDa monomer of the inhibitor. A monoclonal antibody (mab alpha-1) has been described which reacts with the receptor-recognizable form of the inhibitor, the so called transformed alpha2-M (a2-Mt). By screening of a phage display library an **epitope** in the RBD of the inhibitor was identified that reacts with mab alpha-1. Out of 25 phage clones a heptapeptide sequence (S-x1-x2-D-x3-x4-K) was obtained containing identical amino acids in three positions. A consensus peptide (S-R-S-D-P-P-K) was synthesized and found to displace alpha2-Mt from binding to mab alpha-1 and to receptor. The specificity of competition was demonstrated by a reversed peptide and a control antibody. By structural comparison it was found that the consensus heptapeptide mimics a discontinuous conformationally constrained **epitope** present in the RBD of the inhibitor. This is the first report describing the detection of discontinuous **epitopes** by phage display using a short linear peptide.

L8 ANSWER 15 OF 25 MEDLINE
TI Molecular characterization of murine humoral immune response to botulinum neurotoxin type A binding domain as assessed by using **phage antibody** libraries.
AU Amersdorfer P; Wong C; Chen S; Smith T; Deshpande S; Sheridan R; Finnern R; Marks J D
SO INFECTION AND IMMUNITY, (1997 Sep) 65 (9) 3743-52.
Journal code: 0246127. ISSN: 0019-9567.
PY 1997
AB To produce antibodies capable of neutralizing botulinum neurotoxin type A (BoNT/A), the murine humoral immune response to BoNT/A binding domain (H(C)) was characterized at the molecular level by using **phage antibody** libraries. Mice were immunized with BoNT/A H(C), the

Journal code: 1305440. ISSN: 0022-1759.
PY 1996
AB The complete analysis of **epitope** phage display libraries requires sensitive assays capable of detecting peptides expressed on phage that have a wide range of affinities for antibody. We have compared two ELISAs, a 'direct' assay where the phage is captured by an anti-**phage antibody** and the peptide detected by the antibody used for screening, and a 'reverse' assay where the antibody used for screening is first coated on the well and the binding of **phage** detected by the anti-**phage antibody**. We demonstrate, by comparing two fUSE5 derived phage bearing five peptides reacting with the anti-cryptococcal polysaccharide antibody 2H1, that the reverse ELISA is the more sensitive assay. Further, there is a limit in affinity, here around 1 microM, above which phage clones are negative by the direct ELISA. We describe an enhancement of the direct assay by mixing 2H1 with 3-fold excess of anti-heavy or anti-light chain antibody. The resulting polymerization of 2H1 induces an increase in antibody avidity that is responsible for the enhancement. The enhanced direct ELISA allowed rapid and sensitive detection of positive clones and is easily inhibited by free peptide, while the reverse ELISA is not. The enhanced ELISA has also been used successfully for immunological screening of intermediate libraries, allowing detection of rare positive clones that would otherwise be lost. The combination of the three ELISAs, reverse, direct, and enhanced direct, should provide a way to rank phage clones into three classes: very low, low, and high affinity, providing information previously obtained only by the synthesis and testing of many peptides.

L8 ANSWER 18 OF 25 MEDLINE
TI Human antibody responses to HIV type 1 glycoprotein 41 cloned in phage display libraries suggest three major **epitopes** are recognized and give evidence for conserved antibody motifs in antigen binding.
AU Binley J M; Ditzel H J; Barbas C F 3rd; Sullivan N; Sodroski J; Parren P W; Burton D R
SO AIDS RESEARCH AND HUMAN RETROVIRUSES, (1996 Jul 1) 12 (10) 911-24. Journal code: 8709376. ISSN: 0889-2229.
PY 1996
AB A large panel of human Fab fragments against the gp41 subunit of the HIV-1 envelope glycoprotein was isolated by panning six **phage** -displayed **antibody** libraries against recombinant gp41. The libraries were prepared from HIV-1-seropositive donors. Twenty-three Fabs recognizing conformation-dependent determinants on gp41 were isolated. Further selection of libraries against (1) gp41 ligated with Fabs from the initial selection and against (2) a recombinant gp41-containing gp140 protein yielded five additional Fabs. Competition of members of the Fab panel with one another and with previously described antibodies revealed a series of overlapping specificities that were conveniently grouped into three major **epitope** clusters. The majority of Fabs recognized **epitopes** involving residues 649-668 (previously known as the cluster II region), numbered using the Los Alamos LAI sequence. A second set of Fabs reacted with an **epitope** involving residues 584-609 (known as the cluster I region). Another set of Fabs appeared to recognize a third conformational **epitope** that has been termed the cluster III region. This third Fab **epitope** group demonstrated some overlap with both clusters I and II in binding assays. None of the Fabs neutralized HIV-1 laboratory strains at biologically significant concentrations. This tends to support the opinion that a vaccine based on the gp41 molecule has the drawback that neutralizing **epitopes** of gp41 are rare and/or unfavorably presented to the immune system. Analysis of heavy chain sequences revealed common CDR3 motif sequences in several antibodies, which appears to be an interesting consequence of a persistent immune response to conserved antigen structures.

L8 ANSWER 19 OF 25 MEDLINE
TI Defining antibody targets in Streptococcus oralis infection.

AU Burnie J P; Brooks W; Donohoe M; Hodgetts S; al-Ghamdi A; Matthews R C
SO INFECTION AND IMMUNITY, (1996 May) 64 (5) 1600-8.
Journal code: 0246127. ISSN: 0019-9567.
PY 1996
AB Immunoblotting of sera from 12 neutropenic patients with Streptococcus oralis septicemia and 18 patients with endocarditis due to viridans group streptococci revealed immunodominant S. oralis antigens at 85 and 180 kDa. The former cross-reacted with a mouse monoclonal antibody to hsp90. The latter was identified by sequencing positive clones obtained by screening a genomic expression library of S. oralis with pooled sera from patients who had been infected with S. oralis. Antibody eluted from one of these clones reacted with the 180-kDa antigen of S. oralis. Southern blotting confirmed the origin of the clone from S. oralis. The derived amino acid sequence showed 76.2% homology with the PAc protein precursor of Streptococcus mutans and 73.8% homology with the SpaA protein precursor of Streptococcus sobrinus. **Epitope mapping** of the derived amino acid sequence with sera from patients with viridans group streptococcal endocarditis delineated nine **epitopes**. Peptides 1 (TMYPNRQPGSGWDSS) and 2 (WYSLNGKIRAVDVPK), representing two of these **epitopes**, and peptide 3 (YEVEKPLEPAPVAPS), representing the repeat proline region, were synthesized. These three peptides were used to screen a **phage antibody** display library derived from a patient who had recovered from S. oralis infection. Two of the human recombinant antibodies produced (SORAL 3 and SORAL 4 against peptide 3) and a human recombinant antibody (B3.7) against the conserved **epitope** (LKVIRK) of hsp90 gave statistically significant protection, compared with control groups, in a mouse model of lethal S. oralis infection.

L8 ANSWER 20 OF 25 MEDLINE
TI BIAcore as a tool in antibody engineering.
AU Malmborg A C; Borrebaeck C A
SO JOURNAL OF IMMUNOLOGICAL METHODS, (1995 Jun 14) 183 (1) 7-13. Ref: 41
Journal code: 1305440. ISSN: 0022-1759.
PY 1995
AB The BIAcore biosensor provides a simple and rapid approach for analysing recombinant antibodies and **phage** displayed **antibody** libraries. In this review we describe the application of the biosensor in the screening of recombinant antibody fragments, kinetic selection of phage displayed antibodies, characterization and **epitope** **mapping** of monoclonal antibodies and their fragments.

L8 ANSWER 21 OF 25 MEDLINE
TI Identification of novel peptide antagonists for von Willebrand factor binding to the platelet glycoprotein Ib receptor from a phage **epitope** library.
AU South V; Searfoss G H; French S; Cheadle C; Murray E; Howk R; Jaye M; Ricca G A
SO THROMBOSIS AND HAEMOSTASIS, (1995 Jan) 73 (1) 144-50.
Journal code: 7608063. ISSN: 0340-6245.
PY 1995
AB We have constructed a fusion phage **epitope** library in the filamentous bacteriophage fuse5. The library was made by inserting a degenerate oligonucleotide which encodes 15 variable amino acids into the NH2-terminal region of the phage gene III protein. This library, containing over 10(7) different **epitope** bearing phage, has been used in an attempt to identify inhibitors of the von Willebrand factor (vWF)-platelet Glycoprotein Ib interaction. The library was screened with a monoclonal antibody (RG46) that recognizes the GPIb binding domain of vWF (amino acids 445-733). A total of 30 clones falling into 8 classes have been identified that react with the RG46 antibody. Isolates from all 8 classes are positive by immunoblot analysis. The amino acid sequence of the gene III fusion protein from positive clones showed a strong homology to the known RG46 **epitope**. Peptides identified from the screen were synthesized and used to demonstrate that some of the synthetic

spleens were harvested, and single-chain Fv (scFv) **phage antibody** libraries were constructed from the immunoglobulin heavy and light chain variable region genes. Phage expressing BoNT/A binding scFv were isolated by selection on immobilized BoNT/A and BoNT/A H(C). Twenty-eight unique BoNT/A H(C) binding scFv were identified by enzyme-linked immunosorbent assay and DNA sequencing. **Epitope mapping** using surface plasmon resonance in a BIAcore revealed that the 28 scFv bound to only 4 nonoverlapping **epitopes** with equilibrium constants (Kd) ranging from 7.3 x 10(-8) to 1.1 x 10(-9) M. In a mouse hemidiaphragm assay, scFv binding **epitopes** 1 and 2 significantly prolonged the time to neuroparalysis, 1.5- and 2.7-fold, respectively, compared to toxin control. scFv binding to **epitopes** 3 and 4 showed no protection against neuroparalysis. A combination of scFv binding **epitopes** 1 and 2 had an additive effect on time to neuroparalysis, which increased to 3.9-fold compared to the control. The results suggest that there are two "productive" receptor binding sites on H(C) which lead to toxin internalization and toxicity. Blockade of these two **epitopes** with monoclonal antibodies may provide effective immunoprophylaxis or therapy against BoNT/A intoxication.

L8 ANSWER 16 OF 25 MEDLINE
TI Human recombinant antibody fragments specific for a rye-grass pollen allergen: characterization and potential applications.
AU de Lalla C; Tamborini E; Longhi R; Tresoldi E; Manoni M; Siccardi A G; Arosio P; Sidoli A
SO MOLECULAR IMMUNOLOGY, (1996 Sep) 33 (13) 1049-58.
Journal code: 7905289. ISSN: 0161-5890.
PY 1996
AB One of the major allergens from the pollen of perennial rye grass (Lolium perenne), Lol pII, was used to isolate specific antibody fragments from a random combinatorial library displaying a large repertoire of human Fab on filamentous phages. After five panning cycles on recombinant Lol pII immunotubes, **phage** binders were isolated and the **antibody** fragments expressed as soluble Fab molecules in the Escherichia coli periplasm. The DNA sequencing of the clones producing antibodies with the highest binding activity showed three of them to be identical, while one differed by two amino acid substitutions in the heavy chain. The antibody fragments were produced in milligram amounts, affinity-purified and further characterized. They bound the natural allergen as well as the recombinant one, with no cross-reactivity with other allergens contained in the pollen extract of L. perenne. One antibody bound the allergen with Kd = 2.63 x 10(-9) M, as demonstrated by the surface plasmon resonance technique, and was able to compete with a fraction of serum IgE. **Epitope mapping** using synthetic peptides revealed that antigenic domains, located between amino acids 39 and 51 of Lol pII, are recognized by Fab and polyclonal IgE from sera of allergic donors. The Fab fragments inhibited the binding of serum IgE to the allergen. In vitro experiments on whole blood from allergic subjects showed that recombinant Fab fragments had a blocking activity on histamine release from cells challenged with recombinant Lol pII allergen. Thus, serum IgE and recombinant Fab fragments recognize common **epitopes**, although they represent the outcome of different maturation and/or selection processes. Our molecular and functional findings altogether indicate that allergen-specific human antibodies may be useful for the characterization of the antigenic structure of allergens. We conclude that a phage library is a powerful source of anti-allergen human antibodies with high affinity and high specificity. Moreover, these molecules may be potentially innovative reagents for the treatment of atopic allergy.

L8 ANSWER 17 OF 25 MEDLINE
TI Enhancement of ELISAs for screening peptides in **epitope** phage display libraries.
AU Valadon P; Scharff M D
SO JOURNAL OF IMMUNOLOGICAL METHODS, (1996 Oct 16) 197 (1-2) 171-9.

peptides exhibited inhibitory activity towards ristocetin induced binding of vWF to the GPIb receptor. Thus, we have demonstrated that screening a fusion **phage epitope** library with a monoclonal **antibody** that inhibits vWF binding to the GPIb receptor can be a useful tool not only for **mapping** antibody recognizing determinants, but also can serve as a source for identifying novel peptides that are antagonists for vWF binding to the platelet GPIb receptor.

L8 ANSWER 22 OF 25 MEDLINE
TI Characterisation of **epitopes** on human p53 using **phage** -displayed peptide libraries: insights into **antibody**-peptide interactions.
AU Stephen C W; Helminen P; Lane D P
SO JOURNAL OF MOLECULAR BIOLOGY, (1995 Apr 21) 248 (1) 58-78. Journal code: 2985088R. ISSN: 0022-2836.
PY 1995
AB We previously described the use of a phage-displayed library of random hexapeptides to define and localise the **epitope** on the human tumor suppressor protein p53 recognised by the monoclonal antibody PAb240. Here we have extended these results to a further eight anti-p53 monoclonal antibodies and to two further libraries, which display 12-mer and 20-mer peptides, respectively. First, we showed that selection of PAb240 binding clones from the 12-mer and 20-mer libraries gives essentially identical results to those obtained by screening the 6-mer library. Second, we used the 6-mer and 12-mer libraries to define the detailed specificity profiles of six antibodies (DO-1, DO-2, DO-7, Bp53-11, Bp53-12 and Bp53-19), which recognise the same short, highly immunogenic N-terminal segment of p53. Finally, we employed all three libraries to reveal the distinct mechanisms by which PAb421 and PAb122, two monoclonal antibodies that allosterically activate sequence-specific DNA binding by p53, react specifically with the same positively-charged C-terminal segment. In each case the **epitope** locations inferred from the selected sequences were confirmed by probing an array of overlapping synthetic peptides representing the primary sequence of p53. The results emphasise the consequences for **epitope mapping** of screening random, as opposed to antigen-derived, peptide libraries; specifically (1) that comparison of selected sequences reveals the contribution of individual residues to binding energy and specificity; (2) that heteroclitic reactions can lead to definition of a consensus that is related to but distinct from the immunising **epitope** and (3) that isolation of non-immunogen-homologous "mimotope" sequences reveals discrete, alternative ligand structures. The results with PAb421 and PAb122 provide examples where, while selection from the 12-mer and 20-mer libraries leads to isolation of immunogen-homologous sequences, selection from the 6-mer library results in the isolation either of no binding clones (PAb122) or solely of "mimotope" sequences with no discernible homology to the original antigen (PAb421). In addition the results with PAb421 reveal that linear **epitopes** can be longer than previously thought and can be formally discontinuous, consisting of independent contact motifs, which show promiscuous relative positioning.

L8 ANSWER 23 OF 25 MEDLINE
TI Chaperonin assisted **phage** display of **antibody** fragments on filamentous bacteriophages.
AU Soderlind E; Lagerkvist A C; Duenas M; Malmborg A C; Ayala M; Danielsson L; Borrebaeck C A
SO BIO/TECHNOLOGY, (1993 Apr) 11 (4) 503-7. Journal code: 8309273. ISSN: 0733-222X.
PY 1993
AB We have used the GroE chaperonins to assist in the packing of a new phage display vector, pEXmide3. Titers of the packed phagemid increased almost 200-fold from approximately 4 x 10(11) cfu/ml, without coexpression of the GroE proteins, to approximately 7 x 10(13) cfu/ml with their coexpression. Equal titers of non-assisted and assisted phagestocks exhibited the same

PY 1997
AB A review, with 163 refs., discussing antibody **phage** display libraries, expression of whole **antibody** mols., antibodies to viruses, neutralization of virus by recombinant Fab fragment and whole IgG, antibodies to HIV-1, antibodies to the CD4-binding site and other **epitopes** on gp120, antibodies to gp41, and antibody phage display libraries as tools to assess vaccines.

L8 ANSWER 6 OF 25 CA COPYRIGHT 2003 ACS
TI Production of phage-display antibodies for **epitope mapping**
AU Walker, Jenny; Banting, George
SO Methods in Molecular Biology (Totowa, New Jersey) (1996), 66(Epitope Mapping Protocols), 391-405
CODEN: MMBIED; ISSN: 1064-3745
PY 1996
AB A review with 22 refs. The authors present detailed methods for the prepn. and panning of Fab antibody libraries. In addn. to the obvious advantage of obtaining a no. of **epitope**-specific antibodies from a single library, the smaller size of Fab fragments produced with this system may facilitate greater accessibility than whole antibodies to the target antigen. Antibody library construction circumvents the process of hybridoma prodn. and allows new approaches to antibody selection and design. With antibody cloning, one has immediate access to the DNA encoding the Fab fragment of interest. The sequence encoding a Fab fragment that binds to an antigen with low affinity can be manipulated in order to encode a higher affinity antibody.

L8 ANSWER 7 OF 25 CA COPYRIGHT 2003 ACS
TI Defining antibody targets in Streptococcus oralis infection
AU Burnie, J. P.; Brooks, W.; Donohoe, M.; Hodgetts, S.; Al-Ghamdi, A.; Matthews, R. C.
SO Infection and Immunity (1996), 64(5), 1600-8
CODEN: INFIBR; ISSN: 0019-9567
PY 1996
AB Immunoblotting of sera from 12 neuropenic patients with Streptococcus oralis septicemia and 18 patients with endocarditis due to viridans group streptococci revealed immunodominant S. oralis antigens at 85 and 180 kDa. The former cross-reacted with mouse monoclonal antibody to hsp90. The latter was identified by sequencing pos. clones obtained by screening a genomic expression library of S. oralis with pooled sera from patients who had been infected with S. oralis. Antibody eluted from one of these clones reacted with the 180-kDa antigen of S. oralis. Southern blotting confirmed the origin of the clone from S. oralis. The derived amino acid sequence showed 76.2% homol. with the PAc protein precursor of Streptococcus mutans and 73.8% homol. with the SpaA protein precursor of Streptococcus sobrinus. **Epitope mapping** of the derived amino acid sequence with sera from patients with viridans group streptococcal endocarditis delineated nine **epitopes**. Peptides 1 (TMYPNRQPGSGWDSS) and 2 (WYSLNGKIRAVDYPK), representing two of these **epitopes**, and peptide 3 (YEVEKPLEPAPVAPS), representing the repeat proline region, were synthesized. These three peptides were used to screen a **phage antibody** display library derived from a patient who had recovered from S. oralis infection. Two of the human recombinant antibodies produced (SORAL 3 and SORAL 4 against peptide 3) and a human recombinant antibody (B3.7) against the conserved **epitope** (LKVIRK) of hsp90 gave statistically significant protection, compared with control groups, in a mouse model of lethal S. oralis infection.

L8 ANSWER 8 OF 25 CA COPYRIGHT 2003 ACS
TI Characterization of **epitopes** on human p53 using **phage** -displayed peptide libraries: insights into **antibody**-peptide interactions
AU Stephen, Charles W.; Helminen, Paivi; Lane, David P.

antigen specificity and ELISA reactivity, indicating the same frequency of displayed Fab-fragments. While the diversity of antibody libraries depends on the bacterial transformation efficiency, the copy number of each antibody is determined by subsequent amplification of the phage, thus chaperonin assisted phagemid packing in bacteriophage M13 can be used as a general and simple tool to increase the amplification level of expressed Fab fragments. pEXmide3 was developed for display of Fab and single chain Fv-fragments (scFv), using restriction enzymes that do not cut, or cut with low frequencies, in genes encoding immunoglobulin variable domains. The vector allows cloning of genes for the variable domains linking these to predetermined human constant domains or cloning of the entire light and heavy Fab chains. A modification of the pelB leader sequence, with a glutamine to alanine substitution at residue 18, was used for export of the light chain.

L8 ANSWER 24 OF 25 MEDLINE
TI Sequence and TnphoA analysis of a Mycoplasma hyorhinis protein with membrane export function.
AU Yogev D; Watson-McKown R; McIntosh M A; Wise K S
SO JOURNAL OF BACTERIOLOGY, (1991 Mar) 173 (6) 2035-44.
Journal code: 2985120R. ISSN: 0021-9193.
PY 1991
AB Proteins translocated across the single plasma membrane of mycoplasmas (class Mollicutes) represent important components likely to affect several interactions of these wall-less microbes with their respective hosts. However, identification and functional analysis of such proteins is hampered by the lack of mutational systems in mycoplasmas and by a perceived limitation in translating recombinant mycoplasma genes containing UGA (Trp) codons in other eubacteria. Here we directly analyze a gene encoding a Mycoplasma hyorhinis protein capable of promoting its membrane translocation. It was initially detected by screening a recombinant **phage** genomic library with **antibody** from a host with M. hyorhinis-induced arthritis and was localized by Tn5 and deletion mutations affecting expression of antigenic translational products. Sequence analysis of the isolated gene predicted a hydrophilic protein, P101, containing three UGA codons and a putative signal peptide with an uncharacteristic cluster of positively charged amino acids near its C terminus. Nevertheless, lambda::TnphoA transposon mutagenesis of an Escherichia coli plasmid bearing the p101 gene resulted in p101::TnphoA fusions expressing products that could translocate as much as 48 kDa of the P101 sequence (up to the first UGA codon) across the E. coli plasma membrane. Fusion proteins containing mature P101 sequences expressed mycoplasma **epitopes** and were found by cell fractionation and detergent phase partitioning to be integral membrane proteins in E. coli, suggesting a lack of signal peptide cleavage in this system. Importantly, identification of P101 by direct analysis of its export function relied neither on prior identification of the mycoplasmal product nor on complete expression of the product from the cloned mycoplasma gene.

L8 ANSWER 25 OF 25 MEDLINE
TI Antigenic determinant in human coagulation factor IX: immunological screening and DNA sequence analysis of recombinant **phage** **map** a monoclonal **antibody** to residues 111 through 132 of the zymogen.
AU McGraw R; Frazier D; de Serres M; Reisner H; Stafford D
SO BLOOD, (1986 May) 67 (5) 1344-8.
Journal code: 7603509. ISSN: 0006-4971.
PY 1986
AB As an approach to the study of structure-function relationships in the normal and defective forms of human coagulation factor IX, we have begun to develop a series of monoclonal antibodies against specific sites on the protein. Zymogen and activated forms of normal factor IX were used initially as antigen for the preparation of monoclonal antibodies. Recombinant phage were prepared by cloning small (50- to 500-nucleotide) random DNA fragments from the coding region of a factor IX cDNA clone into

the expression vector lambda gt11. Immunological screening of these recombinants with mixtures of monoclonal antibodies identified several immunoreactive phage. Further analysis showed that the monoclonal antibody designated IX-30 was generating the positive signals at a frequency of approximately 1/2,500 recombinants. Subcloning and sequence analysis of the inserted DNA in the immunoreactive phage revealed overlapping in-frame insertions, from which it could be inferred that the site in factor IX recognized by IX-30 is confined to residues 111 through 132 in the light chain. Similar **mapping** with other monoclonal antibodies should provide additional probes for the protein structure of human factor IX.

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